MedicalXpress

Researchers identify key factor that stimulates brain cancer cells to spread

August 18 2009

Researchers funded by the National Institutes of Health have found that the activity of a protein in brain cells helps stimulate the spread of an aggressive brain cancer called glioblastoma multiforme (GBM). In a move toward therapy, the researchers showed that a small designer protein can block this activity and reduce the spreading of GBM cells grown in the laboratory.

GBM is the most lethal form of brain cancer, with about half of patients expected to die within a year of diagnosis. GBM is named for the fact that the cancerous cells have properties of support cells in the brain called glial cells. Rather than simply growing in a single tumor mass, GBM cells tend to migrate throughout the brain, making it difficult to remove them surgically. As the cells spread and multiply, they also tend to become resistant to radiation and chemotherapy.

"Interventions to control the spreading of glioblastoma multiforme have the potential to slow the clinical course of the disease and improve overall survival rates," says Jane Fountain, Ph.D., a program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS). NINDS funded the new study through an initiative that encourages research on why brain tumor cells are so highly invasive and how to therapeutically target these cells.

The study's senior author is Susann Brady-Kalnay, Ph.D., a neuroscientist at Case Western Reserve University in Cleveland and an expert on the development of the retina. For years, she has studied how

cells migrate to their proper places in the developing retina. In particular, she studied how this process is regulated by cell adhesion molecules - proteins at a cell's surface that can keep the cell stuck to its surroundings, or help the cell move. She has shown that a cell adhesion molecule called PTPmu is required for retinal cell migration. Investigating the role of PTPmu in GBM dispersal was a logical extension, she says.

"We know that cell adhesion is important for development, and that there are many parallels between what happens during development and what happens in cancer," says Dr. Brady-Kalnay. For instance, she notes there is some evidence that cancer cells have turned back the developmental clock and reverted to an embryonic stem cell-like state.

In their new study published in Cancer Research, Dr. Brady-Kalnay and her team report that in GBM cancer cells, the PTPmu protein is cut into fragments, a process known as proteolysis. One might expect that the loss of intact PTPmu would simply cause the cells to detach from their surroundings. However, the fragments also appear to act as signals that stimulate the cells to move and to thrive outside of their normal surroundings.

The researchers found the PTPmu fragments in GBM tumors that had been surgically removed from patients and in GBM cells grown in the laboratory. Next, they examined how these fragments affected the migration of GBM cells in a petri dish. They observed that adding more of the intact protein to the cells or treating the cells with a chemical inhibitor of proteolysis reduced the cells' ability to migrate.

Finally, they showed that it is possible to suppress the effect of the fragments, even without restoring the intact PTPmu protein. This last experiment built upon a collaboration between Dr. Brady-Kalnay and Frank Longo, M.D., chair of the neurology department at Stanford University School of Medicine. The two researchers had previously

designed a very small protein, or peptide, capable of attaching to PTPmu and blocking its effects on retinal cell migration. Here, Dr. Brady-Kalnay and her team tested this peptide in GBM cells, and found that it blocked their ability to migrate, too.

The peptide cannot currently be used to treat GBM, because it would be broken down rapidly if it was injected directly into the body. The researchers hope to develop injectable compounds that mimic the peptide, and to test those compounds in animal models of GBM.

More information: Burgoyne AM, Phillips-Mason PJ, Burden-Gulley SM, Robinson S, Sloan AE, Miller RH, Brady-Kalnay SM. "Proteolytic Cleavage of PTPmu Regulates Glioblastoma Cell Migration." *Cancer Research*, published online August 18, 2009.

Source: NIH/National Institute of Neurological Disorders and Stroke